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(54) Antimalarial compositions and methods of treatment using quinidine, artemisinine and its derivatives.

(57) A new and improved antimalarial composition and method of treating malaria is described, which employs a combination with, on the one hand, one of the antimalarial agents Artemisinine, Dihydroartemisinine, Arteether, Artemether, Artesunate and on the other hand, Quinidine and optionally Mefloquine and their pharmaceutically acceptable salts.

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Antimalarial compositions and methods of treatment using Quinidine, Artemisinine and its derivatives

The present invention is concerned with an improved antimalarial composition and methods of treating malaria which employ a combination with on the one hand, one of the antimalarial agents, Artemisinine, Dihydroartemisinine, Arteether, Artemether, Artesunate and on the other hand, the antimalarial agent Quinidine alone or with Mefloquine and/or their pharmaceutically acceptable salts.

The generic names used here and elsewhere herein are taken from "Tropical Diseases Research, Seventh Programme Report", Chapter 2; Malaria, UNDP/WORLD BANK/WHO, Published by WHO, 1985. The generic name of Quinidine is taken from "Acta Leidensia", 55, 21-27, 1987. (E.H.D. Smit (1987) The redescovery of Cichonaalkaloids as antimalaria drugs. Acta Leidensia, 55, 21-27).

Drug-resistant malaria is a serious clinical and public health problem. The malaria parasite Plasmodium falciparum, has developed a versatile capacity of evading the effect of a drug either by genetic manipulation or by nongenetic (adaptive) methods. It has been demonstrated that Chloroquine-resistance in malaria parasites is a stable genetically determined character (D.C. Warhurst (1985). Drug resistance, The Pharmaceutical Journal, No. 23, 689-692). The spread of Plasmodium falciparum resistant to chloroquine and other antimalarial drugs is a major challenge to the health care programme in tropical and subtropical countries (Suphat Noeypatimanond, et al., (1983). Treatment of Plasmodium falciparum malaria with a combination of Amodiaquine and Tetracycline in central Thailand, Trans. R. Soc. Trop. Med. and Hyg. 73 (3), 338-340).

The present combination of antimalarial agents as defined above, and more specifically herein below, permits desirable antimalarial therapy while preventing or delaying the development of resistance.

In an animal study, Peters (W. Peters et al. (1977) The Chemotherapy of rodent malaria XXVII. Studies on Mefloquine (WR 142490). Ann. Trop. Med. and Parasit., 71, 407-418) reported that resistance can be slowed down if an antimalarial compound is administered in combination with certain other antimalarial drugs. Peters LW. Peters (1974), Prevention of drug resistance in rodent malaria by the use of drug mixtures. Bull. W.H.O., 51, 379-383. W. Peters (1984) Drug combination, Handbook of Experimental Pharmacology, Vol. 68/11, Antimalarial drugs (ed. W. Peters and W.H.G. Richards, P.P. Berlin, Heidelberg and New York, Springer-Verlag) also emphasised the use of rational drug combinations for the treatment, but also provide a better therapeutic value. For instance, it has been shown that a triple combination of Mefloquine, Sulfadoxin, and Pyrimethamine delayed resistance development in Plasmodium berghei (B. Merkli, et al., (1980). The inhibitory effect of a drug combination on the development of Mefloquine resistance in Plasmodium berghei. Ann. Trop. Med. and Parasit., 4(1) : 1 - 9).

The use of combinations of different antimalarials is known in malarial chemotherapy. For example, a combination of Amodiaquine and Tetracycline and a combination of Pyrimethamine and Sulphadoxine known as Fansidar have been used in the clinic [Suphat Noeypatimanond, et al., (1983). Treatment of Plasmodium falciparum malaria with a combination of Amodiaquine and Tetracycline in central Thailand, Trans. R. Soc. Trop. Med. and Hyg. 73 (3), 338 -340]. Recently, one more antimalarial combination (Fansimef, Mefloquine, Pyrimethamine and Sulphadoxine) is undergoing clinical trials [Tropical Diseases Research, Seventh Programme Report "Chapter 2; Malaria, UNDP/WORLD BANK/WHO, Published by WHO, 1985].

The use of combinations of Artemisinine, its derivatives and other antimalarial compounds, such as Quinine, has been proposed in the Indian Patent Application 26/BOM/87 and the German Patent Application P 37 15 378. Also the synergistic effect of a combination of Artemisinine and Primaquine is known (Wan Yaode, Cang Qizhong, Pharmacy Bulletin, Vol. 16, No. 1, 1981).

There are no prior reports to our knowledge concerning the clinical use of a combination of Artemisinine, Dihydroartemisinine, Arteether, Artemether, or Artesunate with Quinidine and pharmaceutically acceptable salts thereof.

The present invention concerns a new and improved antimalarial composition which comprises one or more of the compounds Artemisinine, Dihydroartemisinine, Arteether, Artemether, Artesunate in amounts less than the recommended therapeutic dose in combination with Quinidine alone or with Mefloquine or pharmaceutically acceptable salts thereof, also in sub-curative doses.

The present invention is also concerned with an improved method for the treatment of malaria in a mammal, including man, which comprises, in addition to treatment with antimalarial agents such as Quinidine alone or with Mefloquine or pharmaceutically acceptable salts thereof in amounts less than the recommended therapeutic dose, treatment with subcurative doses of Artemisinine, Dihydroartemisine, Arteether, Artemether and/or Artesunate.

Synergistic acitivity against Plasmodium berghei is also found in murine model when either Artemisine

or Dihydroartemisinine or Arteether or Artemether or Artesunate is used in combination with Mefloquine and Quinidine. This triple combination shows extraordinary synergism against rodent malaria.

The antimalarial agents, Artemisinine, Dihydroartemisinine, Arteether, Artemether, Artesunate of the first group of the present invention are known. Artemisinine has been isolated from Artemisia annua L. and subsequently synthesised. It has been used for the treatment of falciparum malaria [H.P. Koch (1981) Qinghasosu: a potent antimalarial from plant origin, Pharmacy International (New Drugs), p. 184-185, Elsevier North Holland Biomedical Press;L.J. Bruce-Chwatt (1982). Qinghaosu: a new antimalarial. British Med. J., 184, 767-768]. The clinical evaluation of the activity of Artemisinine in 2069 patients was reported by Koch in 1981, of which 1511 patients were treated for a vivax malaria [H.P. Koch (1981) Qinghaosu: a potent antimalarial from plant origin, Pharmacy International (New Drugs), p. 184-185, Elsevier North Holland Biomedical Press]. It has also been shown to be active against Chloroquine-resistant strains of Plasmodium falciparum in man[J.B. Jiang et al., (1982). Antimalarial activity of Mefloquine and Qinghaosu. Lancet, ii. 8293, 285-287]. Dihydroartemisinine, Arteether, Artemether, Artesunate are semi-synthetic derivatives of Artemisinine. Their antimalarial activity is disclosed in different WHO reports. [W.H.O. Report of the Scientific Working Group on the Chemotherapy Malaria, TDR/Chemal 3rd Review, 85. 3, Geneva, 3 - 5 June 1985 and references contained therein].

The antimalarial agents, Quinidine and Mefloquine are also known in the literature [W.H. Wernsdorfer (1987). Quinidine in health care in the tropics. Acta Leidensia, 55: 197 -208, W. Peters (1987), Chemotherapy and drug resistance in malaria, Vol: 1, pp 240-242, Vol. 2, pp 790-91, Academic Press Ltd. London].

The clinical value of the present improved formulation in antimalarial therapy is reflected by appropriate animal studies. Typical experimental protocols, in which the ability of the test compound to act as an antimalarial agent was determined even against drug-resistant strains of P. berghei, are found in the specific examples given below.

The present invention is readily carried out. Artemisinine or one of its derivatives as defined above is generally dosed in a mammal in the range of 0.125 to 10 mg/kg x 5 days, each day one single dose. The second antimalarial agent Quinidine alone or with Mefloquine can be dosed separately, in which case the latter will be employed in an amount within (but generally lower) the dosage range and according to regimens (frequency, routes and compositions) as specified for its utility in the prior art, for example, in the references cited above or further cited in the said references.

Preferably and conveniently, Artemisinine or one of its derivatives and the second antimalarial agent of the invention are administered in a single, combined formulation. This can be in a form suitable for parenteral administration, but is preferably in a form suitable for oral administration. The proportion of each drug in the proposed combined dosage form will be in the ratio of the total daily dose of each drug when dosed alone. The combined drugs will be dosed in single or divided doses.

In the preferred oral route of dosage, the amount of Artemisinine for an average adult patient may generally be in the range of 0.2 - 2 g in combination with 200 - 600 mg Quinidine. The amount administered in the second dose may be administered 6 hours after in the range of 0.2 - 2 g of Artemisinine in combination with 100 - 300 mg of Quinidine for 3 more days, each day one single dose.

In a similar manner, combinations can be prescribed for Quinidine with other antimalarial Artemisinine derived agents of the first group. A combination of Dihydroartemisinine (range 0.2 - 1.5 g) with Quinidine (range 200 - 600 mg) may generally be administered to an adult patient followed by a 2nd dose after 6 hours in the range of 0.2 - 1.5 g of Dihydroartemisinine in combination with 200 - 600 mg of Quinidine. The amount administered in the second dose may generally be given for 3 more days, each day single dose.

Again a combination of Arteether (range 0.2 - 1.5 g) together with Quinidine as the first dose may generally be administered to an adult patient. Second dose may be administered 6 hours after the first dose and may contain 0.2 - 1.5g of Arteether plus 200 - 600 mg of Quinidine. The amount administered in the second dose may generally be given for 3 more days, each day single dose. The above mentioned Quinidine doses can also be substituted by the same dose of a mixture of Quinidine and Mefloquine.

The combined compounds are administered alone or in further combination with pharmaceutically acceptable carriers or diluents both orally and parenterally. For oral use, suitable pharmaceutical carriers include inert diluents or fillers, thereby forming dosage forms such as tablets, powders, capsules, and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavourings, binders, excipients and the like.

For example, tablets containing various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard

gelatin capsules, preferred materials therefore include lactose or milk sugar and high molecular weight polyethylene glycols.

For oral formulation the mixture of the compounds can for example be administered in a gelatin capsule. Such formulation could be based on a suitable refined edible oil such as sunflower oil, corn oil, peanut oil, coconut oil or til oil.

The present invention is illustrated by the following examples. It should be, however, understood that the invention is not limited to the specific details of the examples.

Example 1

Synergistic or additive therapeutic effects of sub-curative doses of Artemisinine in combination with sub-curative doses of Quinidine against Chlorquine sensistive Plasmodium berghei infection in Swiss mice.

Biological Evaluation Methodology:

The evaluation of blood-schizontocidal activity "28-day test" described by Raether and Fink [W. Raether and E. Fink (1979). Antimalarial activity of Floxacrine (HOE 991), I Studies on blood schizontocidal action of Floxacrine against P. berghei, P. vinekei and P. cynomolgi, Ann. Trop. Med. and Agrasit 73: 503 - 526] was followed.

Mice: All experiments were carried out in random bred male and female Swiss mice obtained from the Hoechst breeding house at Mulund, Bombay. The animals were free from Eperythrozoon coccoides. The animals received food pellets and water ad lib and were kept at 22 - 25 ° C room temperature.

Parasite: Plasmodium berghei K-173 strain drug-sensitive and P. berghei (NS) moderately resistant to Chloroquine were obtained from London School of Hygiene and Tropical Medicines. The strains produce lethal infection at 1×10^7 parasitized red blood cells per mouse when inoculated intraperitoneally.

Administration of compounds: The compounds were adrninistered orally or sub-cutaneously as per methods described by Raether and Fink [W.Raether and E. Fink (1979). Antimalarial activity of Floxacrine (Hoe 991), I, Studies on blood schizontocidal action of Floxacrine against P. berghei, P. vinekei and P. cynomolgi, Ann. Trop. Ned. and Agrasit 73: 503 - 526], Artemisinine, Dihydroartemisinine and Arteether were homogenized in double refined corn oil and such suspensions were used for sub-cutaneous inoculation in mice. Drugs were administered for 5 days. 1st dosing was done within 2 hours of infection (D + 0) followed by D + 1, D + 2, D + 3 and D + 4.

Observation on the treated mice: The blood smears were prepared at different intervals from D + 4 and continued up to D + 28. Blood smears were drawn from the terminal end of the tail and stained in Giemsa. Mice which were free from P. berghei on D + 28 were considered as completely cured. At least 12 mice were tested for each dosage.

The synergistic or additive therapeutic effect of sub-curative doses of Artemisinine, Dihydroartemisinine, and Arteether, each in combination with sub-curative doses of Quinidine against Chloroquine-sensitive Plasmodium berghei infected mice is shown in Table I when the compounds are orally administered, and in Table II when the compounds are administered sub-cutaneously. These data show that sub-curative doses of Artemisinine, Dihydroartemisinine, and Arteether, each in combination with sub-curative doses of Quinidine cure Chloroquine-sensitive Plasmodium berghei infected mice, when the compounds are administered either orally or sub-cutaneously.

Example 2

Synergistic or additive therapeutic effect of sub-curative doses of Artemisinine in combination with sub-curative doses of Quinidine against Chloroquine-resistant strains of Plasmodium berghei (NS) infected in Swiss mice.

The evaluation of blood-schizontocidal activities was carried out following the procedure described in Example 1, using the Chloroquine resistant strain of P. berghei.

The synergistic or additive therapeutic effect of sub-curative doses of Artemisinine, Dihydroartemisinine, Arteether each in combination with sub-curative doses of Quinidine against Chloroquine-resistant strains of Plasmodium berghei (NS) infection in Swiss mice is shown in Table II when the compounds are administered either orally or sub-cutaneously. These data show that sub-curative doses of Artemisinine,

Dihydroartemisinine, Arteether each in combination with sub-curative doses of Quinidine completely cured against Chloroquine-resistant strains of Plasmodium berghei (NS) infected mice, when the compounds are administered orally or sub-cutaneously.

Example 3

Synergistic or additive potentiation effects of sub-curative doses of Artemisinine or Dihydroartemisinine or Arteether each in combination with sub-curative doses of Mefloquine plus Quinidine against chloroquine-sensitive Plasmodium Berghei K-173 infection in Swiss mice is shwon in Table III, when the compounds are administered either orally or sub-cutaneously. These data show that sub-curative doses of Artemisinine, Dihydroartemisine, Arteether each in combination with sub-curative doses of Mefloquine plus Quinidine completely cure malaria infection in mice when the compounds are administered either orally or sub-cutaneously. These triple combinations are novel and more effective than each drug when they are used alone.

The combination mentioned in the earlier paragraph when tested against Chloroquine-resistant strain of Plasmodium berghei NS also showed high potentiation of activity under similar routes of administration.

Table I

Combination of Artemisinine or Dihydroartemisinine or Arteether with Quinidine against P. berghei K-173				
Formulations	Route	Dose mg/kg x 5	No. of mice per group	infected animals (% cured)
Artemisinine (curative dose)	p.o.	200	12	100
	s.c.	20	12	100
Artemisinine (sub-curative dose)	p.o.	100	20	40
	s.c.	1.0	12	25
Dihydroartemisinine (curative dose)	p.o.	100	12	100
	s.c.	4	12	100
Dihydroartemisinine (sub-curative dose)	p.o.	50	12	50
	s.c.	2.5	12	50
Arteether (curative dose)	p.o.	50	12	100
	s.c.	7.5	16	100
Arteether (sub-curative dose)	p.o.	10	20	0
	s.c.	5	16	68
Formulations	Route	Dose mg/kg x 5	No. of mice per group	infected animals (% cured)
Quinidine (curative dose)	p.o.	200	12	100
	s.c.	50	12	100
Quinidine (sub-curative dose)	p.o.	100	12	0
	s.c.	25	12	40
Artemisinine + Quinidine	p.o.	25 + 100	12	83
	s.c.	2.5 + 50	12	83
Dihydroartemisinine + Quinidine	p.o.	50 + 100	12	100
	s.c.	1.25 + 50	12	100
Arteether + Quinidine	p.o.	10 - 75	20	100
—	s.c.	2.5 + 50	20	100

Table II

Combination of Artemisinine or Dihydroartemisinine or Arteether with Quinidine against P. berghei NS strain (moderately resistant to Chloroquine)				
Formulations	Route	Dose mg/kg x 5	No. of mice per group	infected animals (% cured)
Artemisinine (sub-curative dose)	p.o.	200	12	50
	s.c.	20	12	50
Dihydroartemisinine (sub-curative dose)	p.o.	100	12	50
	s.c.	5	12	50
Arteether (sub-curative dose)	p.o.	15	12	25
	s.c.	5	12	33
Quinidine (sub-curative dose)	p.o.	100	12	0
	s.c.	25	12	33
Artemisinine + Quinidine	p.o.	100 + 100	12	83
	s.c.	10 + 20	12	75
Dihydroartemisinine + Quinidine	p.o.	50 + 100	12	100
	s.c.	5 + 20	12	100
Arteether + Quinidine	p.o.	10 + 100	12	100
—	s.c.	2.5 + 20	12	83

Table III

Combination of Artemisinine or Dihydroartemisinine or Arteether with Quinidine against P. berghei K-173				
Formulations	Route	Dose mg/kg x 5	No. of mice per group	infected animals (% cured)
Artemisinine (curative dose)	p.o.	200	12	100
	s.c.	20	12	100
Artemisinine (sub-curative dose)	p.o.	100	20	40
	s.c.	1.0	12	25
Dihydroartemisinine (curative dose)	p.o.	100	12	100
	s.c.	4	12	100
Dihydroartemisinine (sub-curative dose)	p.o.	50	12	50
	s.c.	2.5	12	50
Arteether (curative dose)	p.o.	50	12	100
	s.c.	7.5	16	100
Arteether (sub-curative dose)	p.o.	10	20	0
	s.c.	5	16	88
Quinidine (curative dose)	p.o.	200	12	100
	s.c.	50	12	100
Quinidine (sub-curative dose)	p.o.	100	12	0
	s.c.	25	12	40
Mefloquine (curative dose)	p.o.	7	12	100
	s.c.	5	12	100
Mefloquine (sub-curative dose)	p.o.	4	12	50
	s.c.	2.5	12	25
Arteether + Mefloquine + Quinidine	p.o.	7.5 + 2.5 + 75	16	100
	s.c.	2.5 + 2.5 + 25	12	100
Artemisinine + Mefloquine + Quinidine	p.o.	25 + 2.5 + 75	8	100
	s.c.	2.5 + 2.5 + 25	8	100
Dihydroartemisinine + Mefloquine + Quinidine	p.o.	40 + 2.5 + 50	12	100
	s.c.	2 + 2.5 + 25	12	100

Claims

1. A pharmaceutical combination with a synergistic action against malaria, which optionally besides customary auxiliaries and vehicles, contains one or more compounds selected from the group Artemisinine, Dihydroartemisinine, Arteether, Artemether and Artesunate, as well as the pharmacologically tolerated salts thereof (group 1), and Quinidine alone or with Mefloquine or their pharmaceutically tolerated salts.

2. A pharmaceutical combination as claimed in claim 1, which contains one or more compounds from the group comprising Artemisinine, Dihydroartemisinine, Arteether, Artemether, Artesunate and Quinidine alone or with Mefloquine.

3. A pharmaceutical combination as claimed in claim 1, which contains one compound from group (1) and Quinidine.

4. A pharmaceutical combination as claimed in claim 1, which contains Artemisinine and Quinidine.

5. A pharmaceutical combination as claimed in claim 1, which contains Dihydroartemisinine and Quinidine.

6. A pharmaceutical combination as claimed in claim 1, which contains Arteether and Quinidine.

7. A pharmaceutical combination as claimed in claim 1, which contains Artemether and Quinidine.

8. A pharmaceutical combination as claimed in claim 1, which contains Artesunate and Quinidine.

9. A pharmaceutical combination as claimed in claim 1, which contains Arteether or Artemisinine or Dihydroartemisinine or Artemether or Artesunate and Mefloquine and Quinidine.

10. The use of a combination of compounds as claimed in claims 1 - 9 for the preparation of pharmaceuticals with a synergistic and/or potentiating activity against malaria.

11. A method for the treatment or the prophylaxis of malaria which employs the administration of a pharmaceutical preparation as claimed in claims 1 - 9.

Claims for the following contracting states: ES, GR.

1. A process for the production of a pharmaceutical combination with a synergistic action against malaria, wherein one or more compounds selected from the group Artemisinine, Dihydroartemisinine, Arteether, Artemether and Artesunate, as well as the pharmacologically tolerated salts thereof (group 1), and Quinidine alone or with Mefloquine or their pharmaceutically tolerated salts are optionally together with customary auxiliaries and vehicles, transformed into a form suitable for administration.

2. A process as claimed in claim 1, wherein the compounds of group (1) are Artemisinine, Dihydroartemisinine, Arteether, Artemether, Artesunate.

3. A process as claimed in claim 1, wherein one compound of group (1) is combined with Quinidine.

4. A process as claimed in claim 1, wherein Artemisinine is combined with Quinidine.

5. A process as claimed in claim 1, wherein Dihydroartemisinine is combined with Quinidine.

6. A process as claimed in claim 1, wherein Arteether is combined with Quinidine.

7. A process as claimed in claim 1, wherein Artemether is combined with Quinidine.

8. A process as claimed in claim 1, wherein Artesunate is combined with Quinidine.

9. A process as claimed in claim 1, wherein Arteether or Artemisinine or Dihydroartemisinine or Artemether or Artesunate is combined with Mefloquine and Quinidine.

10. A method for the treatment or the prophylaxis of malaria which employs the administration of a pharmaceutical preparation produced according to a process as claimed in claims 1 - 9.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 11 8384

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	CHEMICAL ABSTRACTS, vol. 96, no. 21, 1982, page 27, abstract no. 173957c, Columbus, Ohio, US; D.C. WARHURST: "Cinchona alkaloids and malaria", & LANCET 1981, 2(825), 1346 * Abstract * ---	1	A 61 K 31/49
Y	IDEM ---	2-4,9-11	
Y	DIALOG 05625766, MEDLINE 83-89/AUG., no. 85241766; W. PETERS: "The problem of drug resistance in malaria", & PARASITOLOGY, Apr. 1985, 90 (Pt 4), p705-15 * Abstract * -----	2-4,9-11	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	11-01-1990	LEHERTE C.F.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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